REMARKS

Claims 80, 81, and 83-93 remain pending in this application. Applicants reserve the right to file a continuation or divisional application claiming the subject matter of cancelled or withdrawn claims. No new matter has been introduced.

In the Claims

As an initial matter, applicants respectfully direct the Examiner's attention to the amendment filed October 9, 2003, which cancelled claims 1-79 and 82, and not claim 81. Accordingly, the pending claims are claims 80, 81, and 83-93. Claims 80, 81, and 83-93 have been rejected.

Claim Rejections – 35 U.S.C. §112, first paragraph

9) Claims 80-81, and 83-93 stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled with regard to the scope. Specifically, the Examiner contends that the methods of eliciting protective antibodies by administering a group A streptococcal polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate as recited in the claims are not enabled because *in vivo* protective ability of the conjugate vaccine was not shown, nor was *in vivo* protective efficacy of the conjugate vaccine demonstrated by *in vitro* assays. Applicants respectfully disagree.

With respect to enablement, an inventor is required to disclose the invention in a clear and concise manner to enable one skilled in the art to construct a compound and use the same. According to the MPEP 2164.01 (a), factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The instant specification is enabling with respect to the scope of the claims and provides sufficient direction and guidance needed to practice the invention. When determining whether the instant specification is enabling, applicants' assert that the breadth of the claims is sufficiently supported by the specification and the state of the art (See, Examples 1, 6, and 7; Table 4 of the instant specification). Furthermore, the amount of direction provided by the inventor is sufficient to enable the skilled artisan to administer the claimed conjugate containing the epitope responsible for inducing bacterial antibody production to a mammal in order to elicit antibodies that are protective against infection by group A streptococcal bacteria. The instant invention relates to immunogenic compositions comprising group A Streptococcal polysaccharides of formula (I) containing an epitope which induces the formation of bactericidal antibodies. The invention also relates to methods of eliciting antibodies specific to group A streptococcal polysaccharide by administering to a mammal a covalently bound polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate where the polysaccharide component is of Formula (I) and R is a terminal reducing L-rhamnose or D-GlcpNAc and n is 3-50, and the conjugate is administered in an amount sufficient to provide protection against infection by group A streptococcal bacteria. Applicants demonstrate (a) how to make and use the conjugate; (b) that group A polysaccharide antibodies are opsonic or bactericidal; (c) how to administer the conjugate to mammals; and (d) that the conjugate elicits protective effects. In so doing, one skilled in the art would understand how to perform the claimed invention from reading the instant specification without undue experimentation.

From reading pages 12-18 of the instant specification, the skilled artisan would be capable of constructing the claimed conjugate. Example 6 specifically describes conjugating the oxidized GASP to either tetanus toxoid or human serum albumin. The instant specification provides sufficient details and guidance enabling one skilled in the art to make the group A streptococcal polysaccharide-protein conjugate.

Experiments of the instant specification establishes that human sera contains group A polysaccharide antibodies. Further experiments demonstrate that antibodies directed to the group A streptococcal polysaccharide epitope are protective. Applicants demonstrate that

antibodies directed to the group A streptococcal polysaccharide epitope are opsonic, or bactericidal. The bactericidal assays testing human sera demonstrate that the group A polysaccharide antibodies promote opsonophagocytosis (Example 1 and at page 27). Applicants direct the Examiner's attention to Figure 4 which shows that Panel C containing the human serum killed organism growth as there are virtually no colonies present. Figure 5 further demonstrates that the human sera containing group A polysaccharide antibodies are opsonic in other serotypes. These experiments correlate group A polysaccharide antibodies to opsonization.

Applicants' specification, in addition to the Declaration by Francis Michon (previously submitted in response to the Office Action dated April 9, 2003), describes how to make a group A streptococcal polysaccharide-protein conjugate and administer the conjugate to a mammal (see, pgs. 11-16, 20-21). Undue experimentation is not needed to make or use the invention based on the content of the disclosure and further by the Declaration of Francis Michon.

Use of the group A streptococcal polysaccharide conjugate is further demonstrated in Dr. Michon's Declaration. Passive immunization, or immunization through the transfer of specific antibodies from an immunized individual to a non-immunized individual, confirms that group A streptococcal polysaccharide antibodies collected from rabbits immunized with the polysaccharide-tetanus toxoid conjugate protects against a lethal challenge of live Group A streptococci in mice (see, Tables 1-2 of the Declaration). The percentages of mice surviving against group A streptococcus type 6 and 3 challenge were 62% and 87%, respectively. Whereas the control percentages were about 12% and 20%, respectively. These results were found to be statistically significant ($p<0.001$; $p<0.041$).

Active immunization, or immunization of an individual by administering an antigen, used in a similar challenge model confirms that the polysaccharide-tetanus toxoid conjugate administered to mice protects against type 6 and type 14 group A streptococcal bacterial infection. Tables 3 and 4 of Dr. Michon's Declaration demonstrates that 73% and 78%, respectively. The control percentages were about 13% and 23%, respectively. These results were found to be statistically significant ($p=0.003$; $p<0.001$).

From the applicants' disclosure, Dr. Francis Michon's Declaration, and the Sabharwal publication, combined with knowledge in the art, the skilled artisan would have a reasonable expectation that immunization with the claimed group A polysaccharide-protein conjugate would result in passive and active immunity and that it would not require undue experimentation to achieve such a result. Applicants provide one skilled in the art with evidence that immunization with a group A polysaccharide-protein conjugate vaccine elicits antibodies effective for killing group A bacteria.

The Examiner contends that the Sabharwal conjugate is not the same as the claimed conjugate since the Sabharwal group A polysaccharide does not have the same formula or same size as the one recited in the instant claims. However, the polysaccharide-protein conjugate used in the Sabharwal publication is within the scope of the claims (see, item 13 of Dr. Michon's Declaration). As indicated in the Declaration, Francis Michon is co-inventor of the instant application and also co-author of the Sabharwal publication. Contrary to the Examiner's contentions, the group A streptococcal polysaccharide-protein conjugate, where the polysaccharide is of formula (I) and n= 3 to 50, of the Sabharwal publication is within the scope of the claimed group A streptococcal polysaccharide-protein conjugate. Furthermore, the data presented in Dr. Michon's Declaration, provide evidence that the group A polysaccharide - tetanus toxoid conjugate conferred a statistically significant percent survival as a result of passive immunization of the mice pups. Immunization with GASP alone resulted in the survival of only a few pups. Thus, the experiments detailed in the Sabharwal publication further support the instant disclosure that the claimed methods of eliciting protective antibodies reactive to a group A streptococcal polysaccharide are enabled.

The Examiner further contends that "no opsonophagocytic or absorption assay results with the sera obtained by immunizing a mammal with the conjugate recited in the instant claims have been disclosed" (pg. 5; Office Action Nov. 5, 2003). However, applicants have provided several examples of the construction and use of group A streptococcal polysaccharide-protein conjugates. One skilled in the art reading the instant specification would understand how

to make and use the conjugates according to the claimed methods. Based on the unexpected finding that antibodies to group A streptococcus confer resistance to infection (pgs. 19-20) and that high antibody titers result in response to immunization with the claimed conjugate (Table 4), vaccines of the claimed conjugate useful in protecting against group A streptococcal infection are enabled as required by law. Applicants further emphasize that the opsonophagocytic or absorption assay described in the Examples of the instant specification is a model system for demonstrating protection against group A streptococcal disease.

The model system provides a functional example demonstrating the testing of group A streptococcal antibodies in an *in vitro* assay. Pharmacological or biological activity of a compound is relevant to a therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). Applicants remind the Examiner that this reasonable correlation may be evidenced by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence, or any combination thereof. Statistical certainty is not required when applicants provide evidence that a correlation exists between a particular activity and an asserted therapeutic use of a compound, nor is actual evidence of success in treating humans where such a utility is asserted required. All that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

As such, the rabbit data and bactericidal or opsonophagocytic model systems satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. *See Ex parte Forman* 230 USPQ 546 (BBAI 1986); *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1989). Therefore, skilled artisans would understand how to make and use the claimed conjugate for immunizing an individual and recovering the immunogenic antibodies from sera (see pg. 5, ln. 32 – pg. 6, ln.4; pg. 17, ln. 33- pg. 18, ln. 6) after reading the instant specification and what was commonly known in the art.

The Examiner refers to the irrelevance of the "capping phenomenon" to the instantly claimed method; however, applicants respectfully disagree with the Examiner's contention. Antibody titers and bactericidal or protective activity are related by the "capping phenomenon" which is understood to be immunoglobulin cluster formation on the surface of B-cells triggered by specific antigen or cross-reacting agents. The capping action thereby activates antibody production. Contrary to the Examiner's contention, this phenomenon is not restricted to group A Streptococcal –liposome conjugates. Additionally, the claimed conjugate converts the immunogenic response to the polysaccharide from T-cell independent to T-cell dependent, triggering a memory response.

Thus, in view of the above-mentioned arguments, as supported by the Declaration and the Sabharwal, et al. publication previously submitted, one skilled in the art would be enabled to reproduce and successfully use the claimed methods, specifically, perform the bactericidal assays, as well as, the methods of eliciting antibodies protective against infection by group A streptoccocal bacteria as described in the instant specification. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4005US1.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

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By: _____

Evelyn M. Kwon
Registration No. 54,246

Correspondence Address:
MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, NY 10154-0053
(212) 758-4800 Telephone
(212) 751-6849 Facsimile